07/09/90

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CA Structure (1st & 2nd)

07/508,109

redone here

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=> file registry
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY      SESSION
FULL ESTIMATED COST                                    0.25         0.25

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STRUCTURE FILE UPDATES:  HIGHEST RN 131296-01-0
DICTIONARY FILE UPDATES: 06 JAN 91 (910106/ED)  HIGHEST RN 131273-40-0

=> act adaman2?/a
L1                  STR
L2          350 SEA CSS FUL L1

=> file ca
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY      SESSION
FULL ESTIMATED COST                                    0.56         0.81

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FILE COVERS 1967 - 22 Dec 90 (901222/ED)  VOL 113 ISS 26.
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abstract graphic structures.  The AB format DOES NOT display structure
diagrams.


=> s l2
L3          1420 L2

=> s ischemia or ischemic or ischaemia or ischaemic or hypoxia or hypoxic
         11198 ISCHEMIA
          3624 ISCHEMIC
            24 ISCHAEMIA
            31 ISCHAEMIC
          8817 HYPOXIA
          2173 HYPOXIC
L4       20083 ISCHEMIA OR ISCHEMIC OR ISCHAEMIA OR ISCHAEMIC OR HYPOXIA
               OR HYPOXIC

=> s anoxia or anoxic or stroke
          1729 ANOXIA
          1010 ANOXIC
           934 STROKE
L5        3355 ANOXIA OR ANOXIC OR STROKE

=> s l4 or l5
L6       22669 L4 OR L5

=> s alzheimer?
L7        1718 ALZHEIMER?

=> s l6 or l7
L8       24362 L6 OR L7
```

L9 [redacted] & L3 AND L8

=> d l9 1-6 bib ab

L9 ANSWER 1 OF 6
COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

AN CA113(21):184614j
TI Neuroprotective effect of memantine demonstrated in vivo and in vitro
AU Seif el Nasr, Mona; Peruche, Barbara; Rossberg, Christine; Mennel, Hans Dieter; Krieglstein, Josef
CS Inst. Pharmakol. Toxikol., Philipps-Univ.
LO Marburg D-3550, Fed. Rep. Ger.
SO Eur. J. Pharmacol., 185(1), 19-24
SC 1-11 (Pharmacology)
DT J
CO EJPHAZ
IS 0014-2999
PY 1990
LA Eng
AB The protective effects of the anticonvulsant memantine against hypoxic or ischemic damage were studied in a rat model of transient forebrain ischemia and cultured neurons from chick embryo cerebral hemispheres. Ischemia was induced for 10 min by clamping both arteries and lowering the mean arterial blood pressure to 40 mmHg; the rats were allowed to recover for 7 days. Cultured neurons were made hypoxic with 1 mM NaCN added to the incubation medium for 30 min followed by a recovery period of 3 days. The effects of memantine were compared with those produced by a typical non-competitive N-methyl-D-aspartate antagonist, dizocilpine. Similar effects were obtained with both drugs. The drugs reduced the damage caused by transient ischemia to neurons of the hippocampal CA1 subfield. Memantine (10 and 20 mg/kg) had a dose-dependent effect when administered i.p. to rats 1 h before ischemia. Dizocilpine was active at 1 mg/kg. When administered after ischemia, 10 mg memantine/kg protected CA1 neurons against ischemic damage. The 2 drugs protected cultured neurons against hypoxic damage. The lowest effective concn. was 0.1 .mu.M dizocilpine and 1 .mu.M memantine. Thus, memantine possesses neuroprotective activity but is less potent than dizocilpine.

L9 ANSWER 2 OF 6
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AN CA112(19):174876m
TI Amantadine and derivatives as modifiers of x-rays on mammalian cells
AU Alvarez, M. V.; Izquierdo, M. C.
CS Ist. Quim. Fis. "Rocasolano", CSIC
LO Madrid 28006, Spain
SO An. Quim., Ser. C, 85(1), 113-15
SC 8-6 (Radiation Biochemistry)
DT J
CO AQSCD6
IS 0211-1357
PY 1989
LA Spanish
AB The x-ray modifying effects of amantadine (I) and 2 of its derivs. [1-adamantyl-4-nitropyrazole (II) and 1-(3-hydroxy-1-adamantyl)-4-nitropyrazole (III)] were studied in hamster tumor cell cultures under oxic and hypoxic conditions. I showed a moderate radiosensitizing effect under hypoxic conditions whereas II had no radiomodifying effect. III exhibited a radiosensitizing effect under hypoxic conditions even in the

[illegible] with the presence of the OH group.

L9 ANSWER 3 OF 6
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AN CA112(15):138764q
TI Preparation of catechol derivatives for use in disorders of central nervous treatment
AU Fukazawa, Nobuyui; Otsuka, Kengo; Shimada, Shizuo; Miyama, Yukio; Ikeda, Fumiaki; Kaiho, Tatsuo
CS Mitsui Toatsu Chemicals, Inc.
LO Japan
SO Eur. Pat. Appl., 22 pp.
PI EP [illegible] A2 20 Sep 1989
DS R: CH, DE, FR, GB, IT, LI, NL, SE
AI EP 89-302742 20 Mar 1989
PRAI JP 88-63515 18 Mar 1988
JP 88-63516 18 Mar 1988
JP 88-201865 15 Aug 1988
JP 88-201866 15 Aug 1988
IC ICM C07C103-30
ICS A61K031-135; C07C103-26; C07D295-18; C07D207-16; C07D211-60; A61K031-16; A61K031-19; A61K031-215; A61K031-40; A61K031-445
SC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
SX 1
DT [illegible]
CO EPXXDW
PY [illegible]
LA Eng
AB Title compds. I [R1 = H, Ac; R2 = R3R4NCO, Q, R6R7N, CO2R8; R3, R4 = H, alkyl, cycloalkyl, (un)substituted aryl; R5 = H, alkyl (un)substituted aryl, alkoxycarbonyl; X = bond, O, N, CH2; R6, R7 = H, alkyl, alkanoyl; R8 = H, alkyl; n = 1-3; (R1 = R6 = R7 = H and n = 2) and (R1 = R6 = H, R7 = Me, and n = 2) are excluded.], useful for treatment of regressive disorders of central nervous system including senile dementia of the Alzheimer type, are prepd. I also produce nerve growth factor (NGF) in particular tissues of the brain. Dihydrocaffeic acid in EtOH was refluxed in the presence of H2SO4 for 3 h to give 3,4-(HO)2C6H3CH2CH2CO2Et, to which in pyridine was added Ac2O to give I (R1 = Ac; R2 = CO2Et; n = 2). In test for promoting activity for prodn. and secretion of NGF in mouse cells, I (R1 = Ac; R2 = AcNH) at 0.2 mM showed a NGF increase ratio of 12.21.

L9 ANSWER 4 OF 6
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AN CA109(23):207680m
TI The FMOC-ADAM approach to amino acid analysis
AU Betner, I.; Foeldi, P.
CS Pharmacia LKB Biotechnol. AB
LO Bromma S-16126, Swed.
SO [illegible]
SC 9-3 (Biochemical Methods)
DT [illegible]
CO LCGCE7
IS 0888-9090
PY [illegible]
LA Eng
AB Manual and automatic amino acid anal. by HPLC using automated precolumn derivatization with 9-fluorenylmethoxycarbonyl chloride (FMOC) and 1-aminoadamantane (ADAM) is described. Confirmatory expts. are presented, such as studies of reproducibility (CV values in the femtomole range). The limitations of the method are discussed, esp. with respect to the sensitivity, which is .apprx.50 fmol. Results are presented for analyses of protein hydrolyzate

L9 ANSWER 5 OF 6
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AN CA108(11):94948p
TI Preparation of vasopressin fragment derivatives as nootropics for treatment of senility
AU Goto, Giichi; Nagaoka, Akinobu; Wakimasu, Mitsuhiro
CS Takeda Chemical Industries, Ltd.
LO Japan
SO Eur. Pat. Appl., 68 pp.
PI EP 247480 A2 1 Dec 1987
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 86-309800 16 Dec 1986
PRAI JP 85-291474 24 Dec 1985
IC ICM C07K007-06
ICS A61K037-02
SC 34-3 (Amino Acids, Peptides, and Proteins)
SX 2
DT P
CO EPXXDW
PY 1987
LA Eng
AB PGlu-Asp(NHR1)-Cys(H-Cys-OH)-A-D-Lys-B [I; R1 = H, C1-16 alkyl, (substituted) phenyl-C1-3 alkyl; A = amino, C1-6 alkylaminoacid residue; B = OH, amino, amino acid or amide] were prepd. as vasopressin fragment peptides, useful for treatment and prevention of dementia. PGlu-Asn-Cys(H-Cys-OH)-Pro-D-Lys-OH (II) was prepd. using soln.-phase methods, starting from BOC-D-Lys(Z)-OH.DCHA (BOC = tert-butyoxycarbonyl, Z = benzyloxycarbonyl, DCHA = dicyclohexylamine). II reversed cycloheximide-induced amnesia in mice when given intracerebroventricularly at 10 pg-10 ng.

L9 ANSWER 6 OF 6
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AN CA94(11):76956c
TI Dopaminergic agonists and conditioned avoidance response in normoxic or hypoxic rats
AU Saligaut, Christian; Moore, Nicholas; Leclerc, Jean Luc; Boismare, Francis
CS Dep. Pharmacol., Hotel-Dieu
LO Rouen 76031, Fr.
SO Aviat. Space Environ. Med., 52(1), 19-23 ordered 01/09/90.
SC 1-5 (Pharmacodynamics)
DT J
CO ASEMC6
IS 0095-6562
PY 1981
LA Eng
AB The actions of 4 dopaminergic agonists, apomorphine [58-00-4], bromocriptine [25614-03-3], amantadine [768-94-5], piribedil [3605-01-4] on a conditioned avoidance response were studied in normoxic or hypobaric hypoxic rats. Low doses of agonists have no effects in normoxia, but induce an antihypoxic protection (improvement of learning in hypoxia). In contrast, the higher doses impair learning both in normoxia and hypobaric hypoxia. The possibility of an antihypoxic property induced by dopaminergic post-synaptic receptors stimulation is discussed and seems to be the main phenomenon whereas action on other nonspecific sites seems to be responsible for the high dose-induced impairment of learning and of resistance to hypoxia.

=> file registry

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DICTIONARY FILE UPDATES: 06 JAN 91 (910106/ED) HIGHEST RN 131273-40-0

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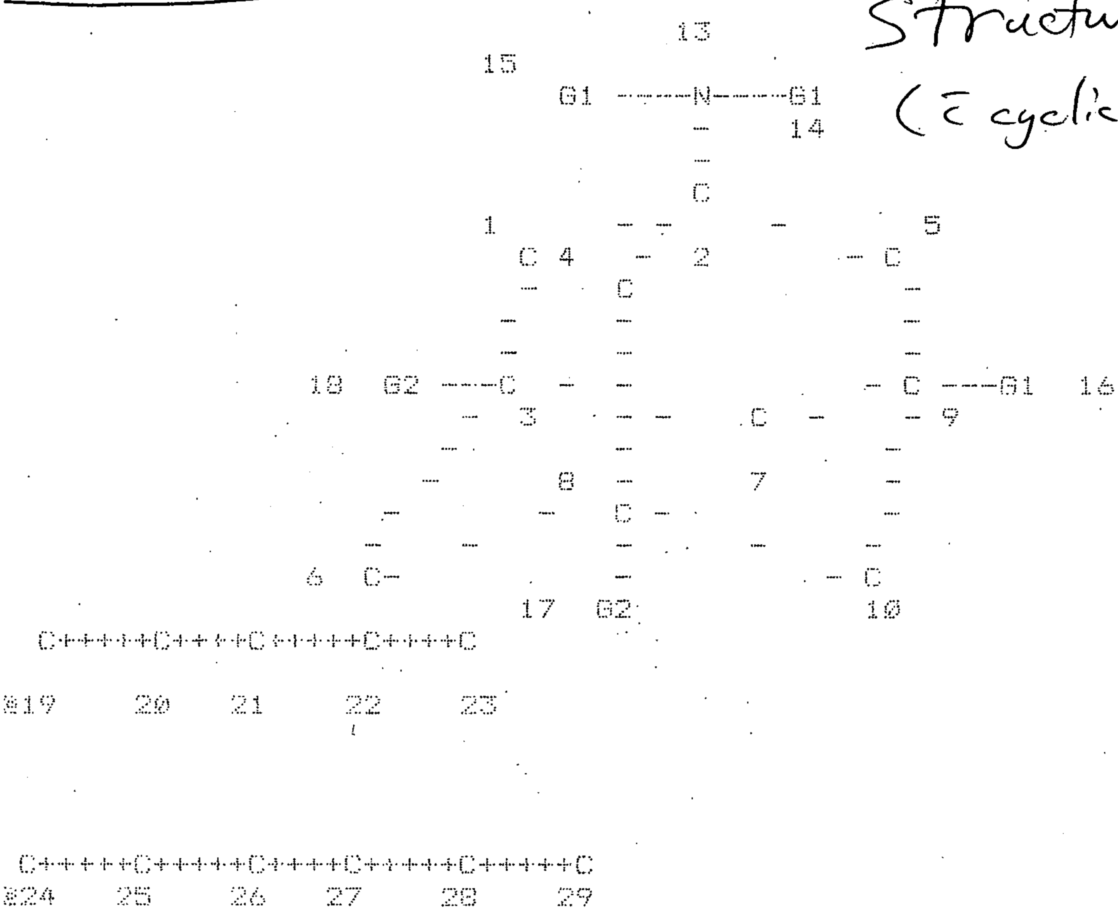
Structure (2nd)
(c cyclic around NOD 13)



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ENTER (DIS), GRA, NOD, BON OR ?:dis
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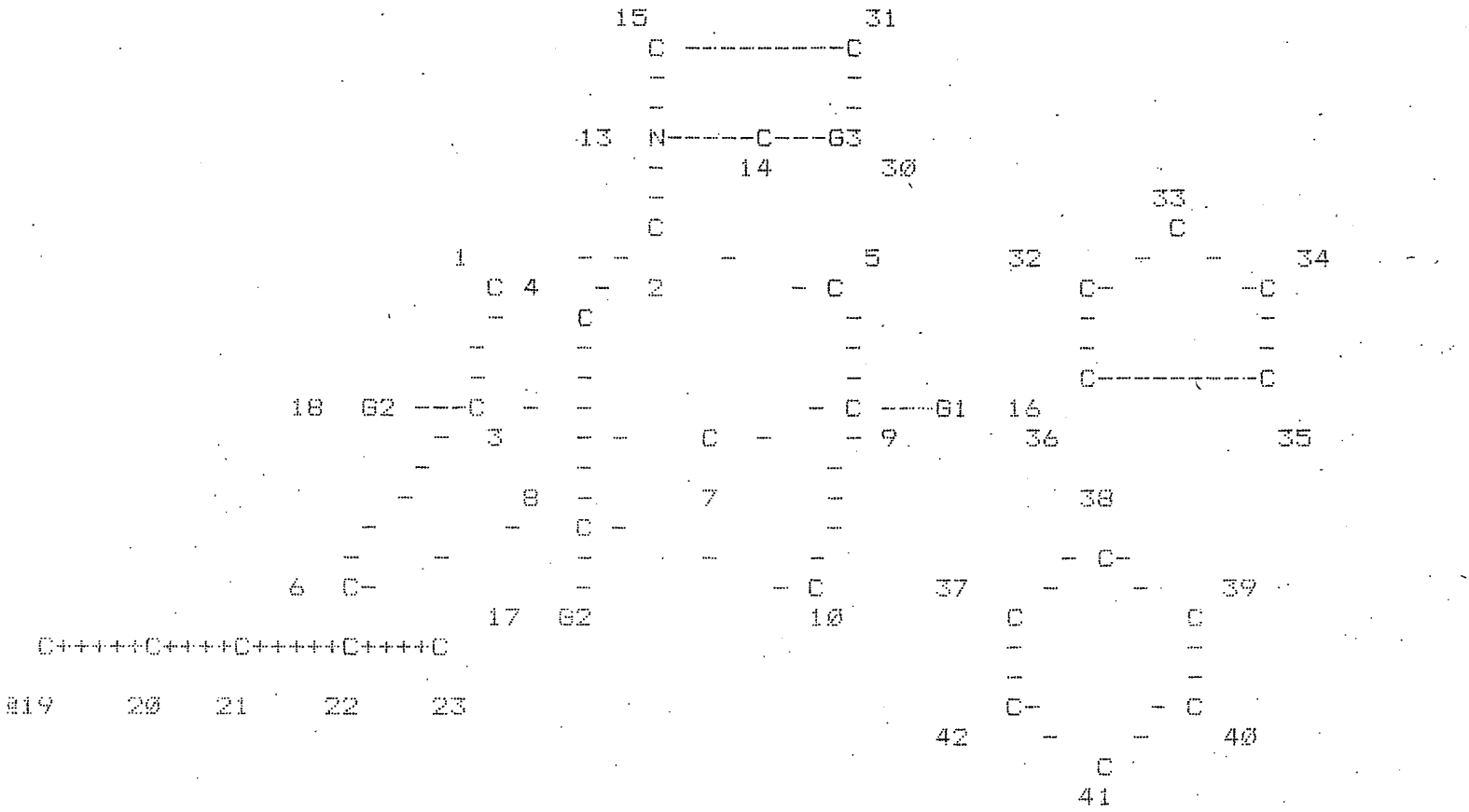


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/32/37
32 IN USE. CHANGE?(Y)/N:y
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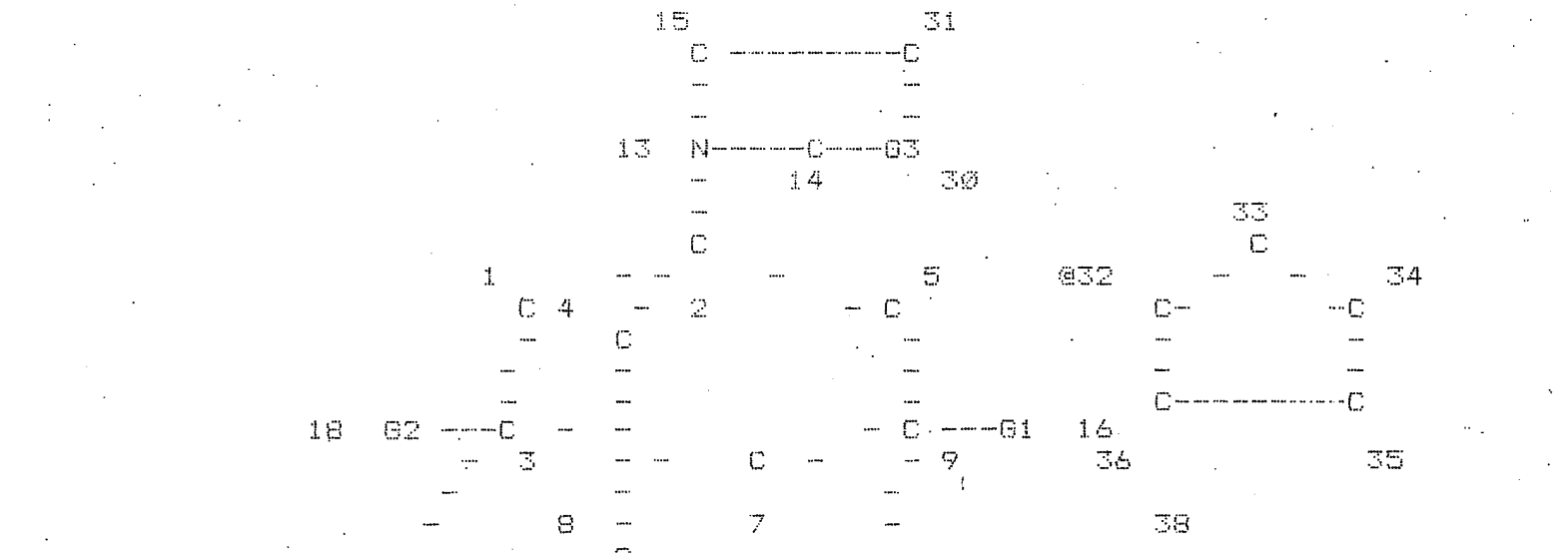

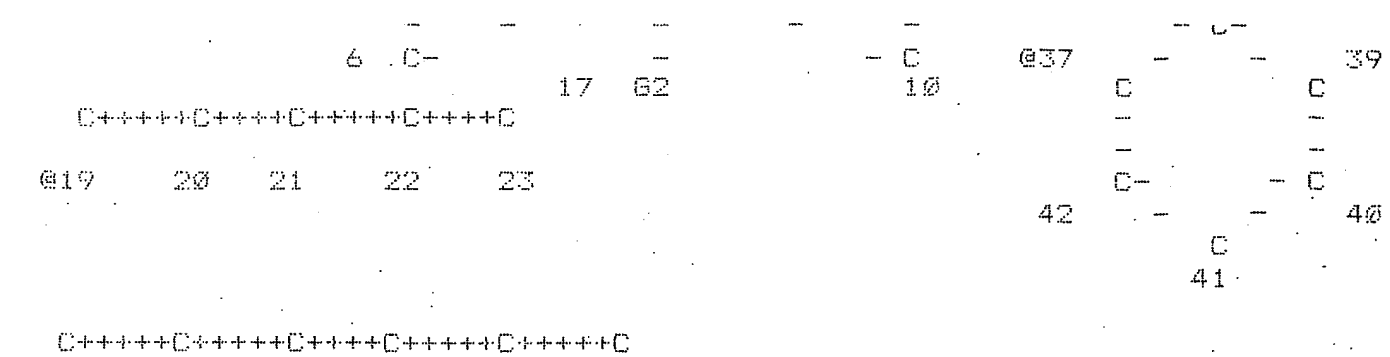


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VAR G2=H/ME/ET/I-PR/N-PR/N-BU/T-BU/S-BU/19/24/PH/32/37
REP G3=(1-2) C
ENTER (DIS), GRA, NOD, BON OR ?:rsp 32
ENTER (DIS), GRA, NOD, BON OR ?:rsp 37,dis sat
NODE ATTRIBUTES: NONE

GRAPH ATTRIBUTES:
RSPEC   2  32  37
NUMBER OF NODES IS  40
ENTER (DIS), GRA, NOD, BON OR ?:end
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=> sav l10 adaman3/q

=> s l10
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SCREENING
SAMPLE SCREEN SEARCH COMPLETED -     30 TO ITERATE
100.0% PROCESSED       30 ITERATIONS                          3 ANSWERS
SEARCH TIME: 00.00.44

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       391 TO      1129
PROJECTED ANSWERS:            3 TO       163

_11            3 SEA SSS SAM L10

=> s l10 css ful
FULL SEARCH INITIATED  14:38:10
FULL SCREEN SEARCH COMPLETED -    583 TO ITERATE
100.0% PROCESSED     583 ITERATIONS                           4 ANSWERS
SEARCH TIME: 00.00.27

_12            4 SEA CSS FUL L10

=> sav l12 adaman4/a

=> d l12 1-4

_12 ANSWER 1 OF 4
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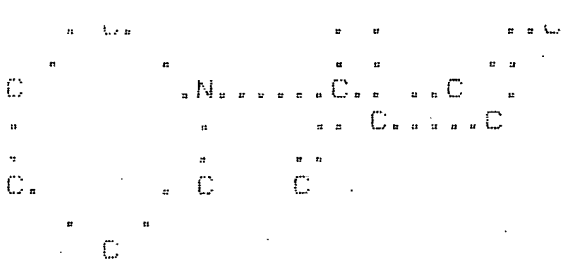
RN   22947-47-3
CN   Piperidine, 1-(1-adamantyl)- (8CI)  (CA INDEX NAME)
FS   3D CONCORD
MF   C15 H25 N
LC   BEILSTEIN, CA
```



1 REFERENCES IN FILE CA (1967 TO DATE)

L12 ANSWER 2 OF 4
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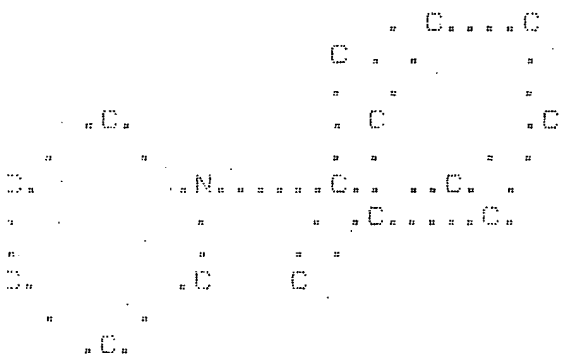
RN 19984-43-1
CN Piperidine, 1-(1-adamantyl)-, hydrochloride (8CI) (CA INDEX NAME)
MF C15 H25 N . Cl H
LC CA, IFICDB, IFIPAT, IFIUDB



@ HCl

2 REFERENCES IN FILE CA (1967 TO DATE)

L12 ANSWER 3 OF 4
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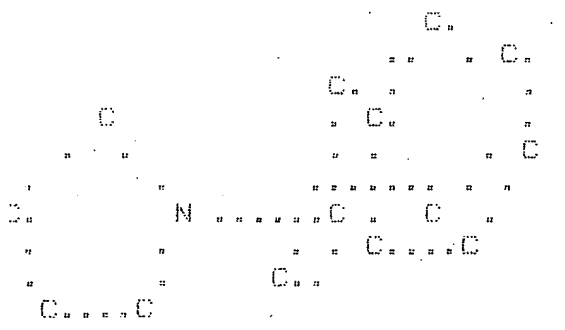
RN 3728-71-0
CN Pyrrolidine, 1-(1-adamantyl)- (7CI, 8CI) (CA INDEX NAME)
FS 3D CONCORD
MF C14 H23 N
LC BEILSTEIN, CAOLD



REFERENCES IN FILE CAOLD (PRIOR TO 1967)
0 REFERENCES IN FILE CA (1967 TO DATE)

L12 ANSWER 4 OF 4
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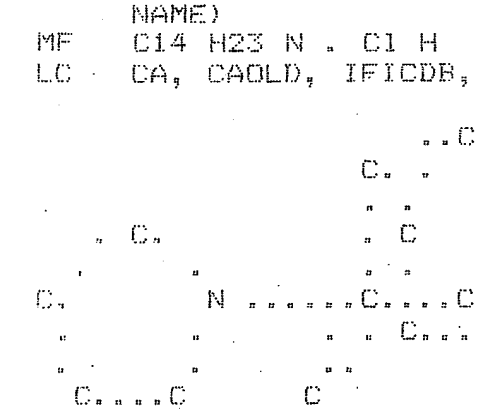
GN Pyrrolidine, 1-(1-adamantyl)-, hydrochloride (9CI, CA INDEX
    NAME)
MF C14 H23 N . Cl H
LC CA, CAOLD, IFICDB, IFIPAT, IFIUDB



@ HCl

REFERENCES IN FILE CAOLD (PRIOR TO 1967)
3 REFERENCES IN FILE CA (1967 TO DATE)

=> file ca

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	127.28	149.69

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CA SUBSCRIBER PRICE	0.00	-2.04

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=> s l12
L13 5 L12

=> d l13 1-5 bib ab

L13 ANSWER 1 OF 5
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AN CA75(11):76237b
TI Antiviral agents. 2. Structure-activity relations of compounds related to 1-adamantanamine
AU Aldrich, Paul E.; Hermann, Edward C.; Meier, Walter E.; Paulshock, Marvin; Prichard, William W.; Synder, Jack Austin; Watts, John C.
CS Exp. Stn., E. I. du Pont de Nemours and Co.
LO Wilmington, Del., USA
SO J. Med. Chem., 14(6), 535-43
SC 24 (Alicyclic Compounds)
DT J
CO JMCMAR
PY 1971
LA Eng
AB A no. of compds. related to 1-adamantamine (I) was prepd. by

N-(1-adamantyl)carboxamides and of the carbamic acid esters. They were tested for the antiviral activity against influenza A virus. None of the N-substituted derivs. of I exhibited greater activity than I itself. Insertion of 1 or more C atoms between N and adamantane nucleus of I caused increased activity. The members of the tricyclo[4.3.1.1]undecane(homoadamantane) system were active. The resolved or racemic mixt. of rimantadine-HCl (II) and .alpha.,.alpha.-dimethyltricyclo[4.3.1.1]undecane-3-methylamine-HCl (III) were the most potent antiviral agents among 87 compds. tested.

L13 ANSWER 2 OF 5
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AN CA71(3):12643r
TI Adamantane and its derivatives. XVIII. Reaction of 1-bromoadamantane with amines
AU Stepanov, F. N.; Stolyarov, Z. E.
CS Kiev. Politekh. Inst.
LO Kiev, USSR
SO Zh. Org. Khim., 5(3), 537-41
SC 24 (Alicyclic Compounds)
DT J
CO ZORKAE
PY 1969
LA Russ
AB Aliphatic primary amines react with 1-bromoadamantane (I) only at 170-80.degree. (sealed tube reaction). Aliphatic secondary amines require 200-10.degree. to react with I. Also prepd. was 1,1'-diadamantylamine. The aromatic amines react with I in 2 ways. Thus PhNH2 gave .apprx.20% N-(adamant-1-yl)aniline (II) and .apprx.7% 4-(adamant-1-yl)aniline. Similarly, o-MeC6H4NH2 reacted with I to give 26.2% 2-methyl-4-(adamant-1-yl)aniline and 4.1% 2-methyl-N-(adamant-1-yl)aniline. However, m-MeC6H4NH2 or p-MeC6H4-NH2 gave only 3-methyl-N-(adamant-1-yl)aniline (III) or 4-methyl-N-(adamant-1-yl)aniline, resp. PhNMe2 also gave only 1 product: 4-(adamant-1-yl)dimethylaniline. The methylation of II or III gave, resp., N-methyl-N-(adamant-1-yl)-aniline and 3-methyl-N-methyl-N-(adamant-1-yl)aniline. The tertiary amines, due to the steric hindrance, are not conjugated through the central N atom.

L13 ANSWER 3 OF 5
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AN CA69(21):86455m
TI Adamantylamines by direct amination of 1-bromoadamantane
AU Krumkalns, Eriks V.; Pfeifer, William
CS Eli Lilly and Co.
LO Greenfield, Indiana, USA
SO J. Med. Chem., 11(5), 1103
SC 24 (Alicyclic Compounds)
DT J
CO JMCMAR
PY 1968
LA Eng
AB Unavailable

L13 ANSWER 4 OF 5
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AN CA69(15):59281v
TI Adamantyl secondary amines
AU Mills, Jack; Krumkalns, Eriks
CS Lilly, Eli, and Co.
SO U.S., 4 pp.
PY US [illegible]

NCL 260268000
SC 28 (Heterocyclic Compounds (More Than One Hetero Atom))
DT P
CO USXXAM
PY 1968
LA Eng
AB Unavailable

L13 ANSWER 5 OF 5

AN CA67(3):11275c
TI 1-Aminoadamantanes
AU Paulshock, Marvin; Watts, John C.
CS du Pont de Nemours, E. I., and Co.
SO U.S., 10 pp.
PI US 3310469 21 Mar 1967
AI US 22 Oct 1963 - 5 May 1966
NCL 167065000
SC 24 (Alicyclic Compounds)
DT P
CO USXXAM
PY 1967
LA Eng
AB Unavailable

=> s L13 and L2
L14 [redacted] (AND) L2

=>

01/08/91 APS

07/508,109

```
=>
s  ischemia or ischemic or ischaemia or ischaemic or hypoxic or hypoxia or anoxi
a or anoxic or stroke or  strokes
            926 ISCHEMIA
           1352 ISCHEMIC
            198 ISCHAEMIA
            315 ISCHAEMIC
            333 HYPOXIC
            523 HYPOXIA
08 JAN 91 09:14:24          U.S. Patent & Trademark Office          P0013
            343 ANOXIA
            256 ANOXIC
          70782 STROKE
          17351 STROKES
L7        77929 ISCHEMIA OR ISCHEMIC OR ISCHAEMIA OR ISCHAEMIC OR HYPOXIC OR H
                YPOXIA OR ANOXIA OR ANOXIC OR STROKE OR  STROKES

=> s alzheimer or alzheimers or alzheimer's
MISMATCHED QUOTE 'ALZHEIMER'S'

=> s alzheimer?
L8          352 ALZHEIMER?

=> s l8 and l7
L9           92 L8 AND L7

08 JAN 91 09:16:00          U.S. Patent & Trademark Office          P0014
=> s adamantane? or ?adamantane or ?adamantanes
            845 ADAMANTANE?
            900 ?ADAMANTANE
            122 ?ADAMANTANES
L10        1063 ADAMANTANE? OR ?ADAMANTANE OR ?ADAMANTANES

=> s l10 and l9
L11           1 L10 AND L9

=> d l11

1.  4,873,331, Oct. 10, 1989, Noradamantyl-carboxylic acid piperazinoalkyl
esters; Wayne E. Childers, Jr., et al., 544/295, 357, 360, 394

=> d l11 ab
08 JAN 91 09:18:27          U.S. Patent & Trademark Office          P0015

US PAT NO:      4,873,331                          L11: 1 of 1

ABSTRACT:
The compounds of the following structural formula posses useful anxiolytic,
antidepressant, antipsychotic and learning and memory enhancement properties:
##STR1## in which R.sup.1 is 3-noradamantyl;
 n is 0 or 1;
 X is --CO.sub.2 --, --O.sub.2 C-- or --OCO.sub.2 --;
 m is 1, 2, 3, 4, or 5;
and
 R.sup.2 is phenyl, benzyl, pyridinyl, pyrimidinyl, pyrazinyl or substituted
  phenyl or benzyl in which the substituent is alkyl, alkoxy, halo, cyano,
  nitro or trifluoromethyl;
or a pharmaceutically acceptable salt thereof.
```

```
=> s adamant?
L12          3107 ADAMANT?

=> s l12 not l10
L13          2202 L12 NOT L10

=> s l13 and l9
L14             3 L13 AND L9

=> s l14 not l11
L15             3 L14 NOT L11

=> d l15 1-3

1.  4,906,779, Mar. 6, 1990, N,N'-disubstituted guanidines and their use as
excitatory amino acid antagonists; Eckard Weber, et al., 564/238

08 JAN 91 09:20:35          U.S. Patent & Trademark Office          P0017
2.  4,789,674, Dec. 6, 1988, Bi-2H-pyrroli(di)nediones; Romeo Paioni,
514/227.8, 232.2, 252, 316, 333, 422; 544/58.5, 141, 357, 372; 546/187, 256;
548/519

3.  4,758,575, Jul. 19, 1988, Bi-2H-pyrroli(di)nediones; Romeo Paioni,
514/316, 326, 409, 422; 544/58.5, 58.6, 111, 141, 357, 372; 546/187, 200;
548/408, 519

=> d l15 1-3 ti ab

JS PAT NO:      4,906,779                                  L15: 1 of 3
ITLE:           N,N'-disubstituted guanidines and their use as excitatory
                  amino acid antagonists

ABSTRACT:
Disubstituted guanidines, e.g., N,N'-di-m-tolyl guanidine,
N,N'-di-o-ethylphenyl guanidine, N,N'-di-m-ethylphenyl guanidine, and
08 JAN 91 09:20:55          U.S. Patent & Trademark Office          P0018

JS PAT NO:      4,906,779                                  L15: 1 of 3
N,N'-di-o-iodophenyl-guanidine, exhibit a high binding affinity to
phenylcyclidine (PCP) receptors. These guanidine derivatives act as
non-competitive blockers to glutamate induced responses of the NMDA receptor
by acting as blockers for the ion channel of the NMDA receptor-ion channel
complex. These compounds thus exert a neuroprotective property and are useful
in the therapeautic treatment of neuronal loss in [redacted], [redacted],
hypoglycemia, and brain and spinal cord trauma as well as being useful for
the treatment of epilepsy, [redacted]'s disease, Amyotrophic Lateral
Sclerosis, Huntington's disease, Down's Syndrome and other neurodegenerative
disorders.

JS PAT NO:      4,789,674                                  L15: 2 of 3
ITLE:           Bi-2H-pyrroli(di)nediones
08 JAN 91 09:21:06          U.S. Patent & Trademark Office          P0019

JS PAT NO:      4,789,674                                  L15: 2 of 3

ABSTRACT:
Novel Substituted tetrahydro-, hexahydro- and
octahydro-[3,4'-bi-2H-pyrrole]-2,2'-diones of the formula ##STR1## in which
each of R.sub.1 and R.sub.2 represents a carboxy-lower alkyl radical, or an
unsubstituted carbamoyl-lower alkyl radical or a carbamoyl-lower alkyl
radical which is N-mono- or N,N-di-substituted by lower alkyl, hydroxy-lower
alkyl, lower alkoxy-lower alkyl, amino-lower alkyl, N-mono- or N,N-di-lower
alkylamino-lower alkyl, or by N,N-alkyleneamino-lower alkyl optionally
substituted (in the alkyleneamino radical) by lower alkoxycarbonyl and by oxo
or hydroxy, or N,N-alkenylene-amino-lower alkyl optionally substituted (in
```

additionally by hydroxy, or N,N-(aza-, N'-lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia)alkyleneamino-lower alkyl, each of which has from 4 to 8 ring members, carbamoyl-lower alkyl, N-mono- or N,N-di-lower

alkylcarbamoyl-lower alkyl, 3- to 8-membered cycloalkyl, dicycloalkyl or tricycloalkyl, or by phenyl-lower alkyl which is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, or represents a carbomoyl-lower alkyl radical which is disubstituted by alkylene optionally substituted by lower alkoxycarbonyl and by oxo or hydroxy, or by alkenylene optionally substituted by lower alkoxycarbonyl and optionally additionally by hydroxy, or by aza-, N'-lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia-alkylene, each of which has from 3 to 7 chain members, each of R.sub.3, R.sub.4, R.sub.5 and R.sub.6 represents hydrogen or lower alkyl, or R.sub.3 and R.sub.4 together and/or R.sub.5 and R.sub.6 together represent a 4- to 8-membered alkylene radical, and each of R.sub.7, R.sub.8, R.sub.9 and R.sub.10 represents hydrogen, or R.sub.7 together with R.sub.8 and/or R.sub.9 together with R.sub.10 represent in each case an additional bond, and their salts, have nootropic activity and can be used as active ingredients in medicaments. They are manufactured, for

example, as follows: in a compound of the formula ##STR2## in which R'.sub.1 represents a group that can be converted into a radical R.sub.1 and R'.sub.2 represents a radical R.sub.2 or a group that can be converted into the radical R.sub.2, or in a salt thereof, R'.sub.1 is converted into a group R.sub.1 and, optionally, a radical R'.sub.2 that can be converted into R.sub.2 is converted into a group R.sub.2.

TITLE: Bi-2H-pyrroli(di)nediones

ABSTRACT:
Novel substituted tetrahydro-, hexahydro- and octahydro-[3,4'-bi-2H-pyrrole]-2,2'-diones of the formula ##STR1## in which each of R.sub.1 and R.sub.2 represents a carboxy-lower alkyl radical, or an unsubstituted carbamoyl-lower alkyl radical or a carbamoyl-lower alkyl

radical which is N-mono- or N,N-di-substituted by lower alkyl, hydroxylower alkyl, lower alkoxy-lower alkyl, amino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, or by N,N-alkyleneamino-lower alkyl optionally substituted (in the alkyleneamino radical) by lower alkoxycarbonyl and by oxo or hydroxy, or N,N-alkenyleneamino-lower alkyl optionally substituted (in the alkenyleneamino radical) by lower alkoxycarbonyl and optionally additionally by hydroxy, or N,N-(aza-, N'-lower alkylaza- or N'-lower alkanoylaza-, oxa- or thia)alkyleneamino-lower alkyl, each of which has from 4 to 8 ring members, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, 3- to 8-membered cycloalkyl, dicycloalkyl or tricycloalkyl, or by phenyl-lower alkyl which is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, or represents a carbamoyl-lower alkyl radical which is disubstituted by alkylene optionally substituted by lower alkoxycarbonyl and by oxo or hydroxy, or by alkenylene optionally substituted by lower alkoxycarbonyl and optionally additionally by

hydroxy, or by aza-, N40 -lower alkylaza-or N'-lower alkanoylaza-, oxa- or thia-alkylene, each of which has from 3 to 7 chain members, each of R.sub.3, R.sub.4, R.sub.5 and R.sub.6 represents hydrogen or lower alkyl, or R.sub.3 and R.sub.4 together and/or R.sub.5 and R.sub.6 together represent a 4- to 8-membered alkylene radical, and each of R.sub.7, R.sub.8, R.sub.9 and

together with R.sub.1Ø represent in each case an additional bond, and their salts, have nootropic activity and can be used as active ingredients in medicaments. They are manufactured, for example, as follows: in a compound of the formula ##STR2## in which R'.sub.1 represents a group that can be converted into a radical R.sub.1 and R'.sub.2 represents a radical R.sub.2 or a group that can be converted into the radical R.sub.2, or in a salt thereof, R'.sub.1 is converted into a group R.sub.1 and, optionally, a radical R'.sub.2 that can be converted into R.sub.2 is converted into a group R.sub.2.

JS PAT NO: 4,758,575 L15: 3 of 3

_A Eng
OS CJAOAC 01/09/91

CA Structure(1st) 07/508,109

redone on other search

=> file registry
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	28.98	29.23

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.36	-1.36

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STRUCTURE FILE UPDATES: HIGHEST RN 131296-01-0
DICTIONARY FILE UPDATES: 06 JAN 91 (91106/ED) HIGHEST RN 131273-40-0

=> structure
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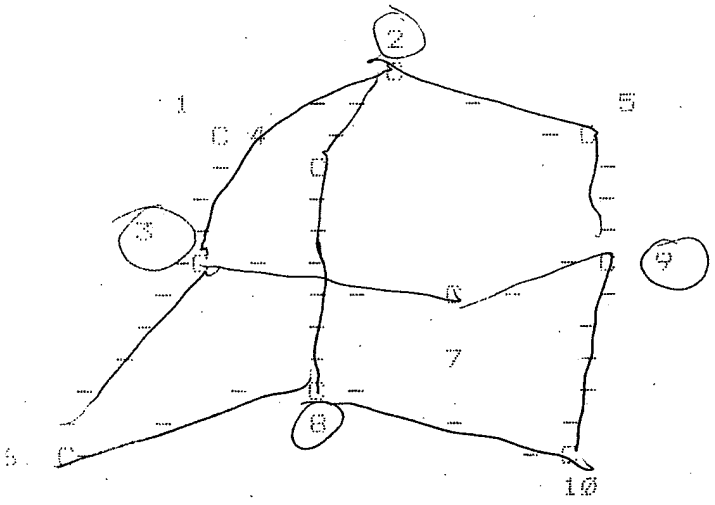

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ENTER (DIS), GRA, NOD, BON OR ?:dis

                    13
          15
              G1 -----N-----G1
                        -   14
                        -
                        C
          1         - -       -         5
            C 4     -   2           - C
            -       C                   -
           -        -                   -
           -        -                   -
18  G2 ----C   -    -                 - C ---G1  16
         -   3      - -      C   -       - 9
      -              -                   -
        -          8 -        7          -
     -             - C -                 -
    -     -         -          -        -
6   C-              -                 - C
              17   G2                   1Ø

ENTER (DIS), GRA, NOD, BON OR ?:


ENTER (DIS), GRA, NOD, BON OR ?:dis

                                  13
                        15
                            G1 -----N----G1
                                       -   14
                                       -
                                       C
                        1         - -       -         5
                          C 4     -   2           - C
                          -       C                   -
                         -        -                   -
                         -        -                   -
                18  G2 ----C   -    -                 - C ---G1  16
                         -   3      - -      C   -       - 9
                      -             -                   -
                     -          8   -        7          -
                   -             - C -                 -
                  -     -         -          -        -
                6   C-              -                 - C
                          17   G2                     1Ø
  C+++++C+++++C+++++C+++++C+++++C

Ø19     2Ø    21     22     23


  C+++++C+++++C+++++C+++++C+++++C
Ø24    25     26     27     28     29

/AR G2=N/ME/ET/I-PR/N-PR/N-BU/I-BU/S-BU/T-BU/19/24
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NODE ATTRIBUTES: NONE

GRAPH ATTRIBUTES:
RSPEC   2
NUMBER OF NODES IS  27
ENTER (DIS), GRA, NOD, BON OR ?:end
_12  STRUCTURE CREATED

=> [redacted]

=> s 112 css ful
FULL SEARCH INITIATED   9:06:14
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FULL SCREEN SEARCH COMPLETED -   6202 TO ITERATE
 23.3% PROCESSED     1444 ITERATIONS                    41 ANSWERS
 44.0% PROCESSED     2730 ITERATIONS                   150 ANSWERS
 65.1% PROCESSED     4036 ITERATIONS                   246 ANSWERS
 82.4% PROCESSED     5109 ITERATIONS                   299 ANSWERS
 93.1% PROCESSED     5773 ITERATIONS                   332 ANSWERS
 98.0% PROCESSED     6080 ITERATIONS                   348 ANSWERS
100.0% PROCESSED     6202 ITERATIONS                   350 ANSWERS
SEARCH TIME: 00.02.21

_13          350 SEA CSS FUL L12    SAV  L13 adanan2/a

=> fil ca
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY     SESSION
FULL ESTIMATED COST                          126.40      155.63

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FILE COVERS 1967 - 22 Dec 90 (901222/ED)  VOL 113 ISS 26.
All OFFLINE Prints or Displays, use the ABS or ALL formats to obtain
abstract graphic structures.  The AB format DOES NOT display structure
diagrams.


=> s ischemia or ischemic or ischaemia or ischaemic or hypoxia or hypoxic
         11190 ISCHEMIA
          3624 ISCHEMIC
            24 ISCHAEMIA
            31 ISCHAEMIC
          8817 HYPOXIA
          2173 HYPOXIC
L14       20083 ISCHEMIA OR ISCHEMIC OR ISCHAEMIA OR ISCHAEMIC OR HYPOXIA
                OR HYPOXIC

=> s anoxic or anoxia or stroke
          1010 ANOXIC
          1729 ANOXIA
           934 STROKE
_15        3355 ANOXIC OR ANOXIA OR STROKE

=> s l14 or l15
_16       22669 L14 OR L15

=> s alzheimer?
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=> s l17 and l13
          1470 L13
L18          3 L17 AND L13

=> s l16 and l13
          1470 L13
L19          3 L16 AND L13

=> s l16 and l17
L20         25 L16 AND L17

=> s l18 not l19
L21          3 L18 NOT L19

=> d l18 1-3
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So got to search L13 in CA file (Search done improperly; see other newer search)

BIB AB

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L18 ANSWER 1 OF 3
COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

AN    CA112(15):138764q
TI    Preparation of catechol derivatives for use in disorders of central
      nervous treatment
AU    Fukazawa, Nobuyui; Otsuka, Kengo; Shimada, Shizuo; Miyama, Yukio;
      Ikeda, Fumiaki; Kaiho, Tatsuo
CS    Mitsui Toatsu Chemicals, Inc.
LO    Japan
SO    Eur. Pat. Appl., 22 pp.
PI    EP 333522  A2  20 Sep 1989
DS    R:  CH, DE, FR, GB, IT, LI, NL, SE
AI    EP 89-302742  20 Mar 1989
PRAI  JP 88-63515  18 Mar 1988
      JP 88-63516  18 Mar 1988
      JP 88-201865  15 Aug 1988
      JP 88-201866  15 Aug 1988
IC    ICM  C07C103-30
      ICS  A61K031-135; C07C103-26; C07D295-18; C07D207-16; C07D211-60;
           A61K031-16; A61K031-19; A61K031-215; A61K031-40; A61K031-445
SC    25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
SX    1
DT    P
CO    EPXXDW
PY    1989
LA    Eng

L18 ANSWER 2 OF 3
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AN    CA109(23):207680m
TI    The FMOC-ADAM approach to amino acid analysis
AU    Betner, I.; Foeldi, P.
CS    Pharmacia LKB Biotechnol. AB
LO    Bromma S-16126, Swed.
SO    LC-GC, 6(9), 832, 834, 836, 838-40
SC    9-3 (Biochemical Methods)
DT    J
CO    LCGCE7
IS    0888-9090
PY    1988
LA    Eng

L18 ANSWER 3 OF 3
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AN    CA108(11):94948p
```

32-36

37-42

treatment of senility
AU Goto, Giichi; Nagaoka, Akinobu; Wakimasu, Mitsuhiro
CS Takeda Chemical Industries, Ltd.
LO Japan
SO Eur. Pat. Appl., 60 pp.
PI EP 227410 A2 1 Jul 1987
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 86-309800 16 Dec 1986
PRAI JP 85-291474 24 Dec 1985
IC ICM C07K007-06
ICS A61K037-02
SC 34-3 (Amino Acids, Peptides, and Proteins)
SX 2
DT P
CO EPXXDW
PY 1987
LA Eng

=> d l10 1-3 ti ab

L10 ANSWER 1 OF 3
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TI Preparation of catechol derivatives for use in disorders of central nervous treatment
AB Title compds. I [R1 = H, Ac; R2 = R3R4NCO, Q, R6R7N, CO2R8; R3, R4 = H, alkyl, cycloalkyl, (un)subsituted aryl; R5 = H, alkyl (un)substituted aryl, alkoxycarbonyl; X = bond, O, N, CH2; R6, R7 = H, alkyl, alkanoyl; R8 = H, alkyl; n = 1-3; (R1 = R6 = R7 = H and n = 2) and (R1 = R6 = H, R7 = Me, and n = 2) are excluded.], useful for treatment of regressive disorders of central nervous system including senile dementia of the Alzhemer type, are prepd. I also produce nerve growth factor (NGF) in particular tissues of the brain. Dihydrocaffeic acid in EtOH was refluxed in the presence of H2SO4 for 3 h to give 3,4-(HO)2C6H3CH2CH2CO2Et, to which in pyridine was added Ac2O to give I (R1 = Ac; R2 = CO2Et; n = 2). In test for promoting activity for prodn. and secretion of NGF in mouse cells, I (R1 = Ac; R2 = AcNH) at 0.2 mM showed a NGF increase ratio of 12.21.

L10 ANSWER 2 OF 3
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TI The FMOC-ADAM approach to amino acid analysis
AB Manual and automatic amino acid anal. by HPLC using automated precolumn derivatization with 9-fluorenylmethoxycarbonyl chloride (FMOC) and 1-aminoadamantane (ADAM) is described. Confirmatory expts. are presented, such as studies of reproducibility (CV values in the femtomole range). The limitations of the method are discussed, esp. with respect to the sensitivity, which is .apprx.50 fmol. Results are presented for analyses of protein hydrolyzate samples from Notechis II (a protein isolated from an Australian snake) and from victims of Alzheimer's disease.

L10 ANSWER 3 OF 3
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TI Preparation of vasopressin fragment derivatives as nootropics for treatment of senility
AB PGlu-Asp(NHR1)-Cys(H-Cys-OH)-A-D-Lys-B [I; R1 = H, C1-18 alkyl, (substituted) phenyl-C1-3 alkyl; A = amino, C1-6 alkylaminoacid residue; B = OH, amino, amino acid or amide] were prepd. as vasopressin fragment peptides, useful for treatment and prevention of dementia. PGlu-Asn-Cys(H-Cys-OH)-Pro-D-Lys-OH (II) was prepd. using soln.-phase methods, starting from BOC-D-Lys(Z)-OH.DCHA (BOC = tert-butyoxycarbonyl, Z = benzyloxycarbonyl, DCHA =

mice when given intracerebroventricularly at 10 pg-10 ng.

=> d 119 1-3

L19 ANSWER 1 OF 3
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AN CA113(21):184614j
TI Neuroprotective effect of memantine demonstrated in vivo and in vitro
AU Seif el Nasr, Mona; Peruche, Barbara; Rossberg, Christine; Mennel, Hans Dieter; Krieglstein, Josef
CS Inst. Pharmakol. Toxikol., Philipps-Univ.
LO Marburg D-3550, Fed. Rep. Ger.
SO Eur. J. Pharmacol., 185(1), 19-24
SC 1-11 (Pharmacology)
DT J
CO EJPHAZ
IS 0014-2999
PY 1990
LA Eng

L19 ANSWER 2 OF 3
COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

AN CA112(19):174876m
TI Amantadine and derivatives as modifiers of x-rays on mammalian cells
AU Alvarez, M. V.; Izquierdo, M. C.
CS Ist. Quim. Fis. "Rocasolano", CSIC
LO Madrid 28006, Spain
SO An. Quim., Ser. C, 85(1), 113-15
SC 6-6 (Radiation Biochemistry)
DT J
CO AQSB06
IS 0211-1357
PY 1989
LA Span

L19 ANSWER 3 OF 3
COPYRIGHT (C) 1991 AMERICAN CHEMICAL SOCIETY

AN CA94(11):76956c
TI Dopaminergic agonists and conditioned avoidance response in normoxic or hypoxic rats
AU Saligaut, Christian; Moore, Nicholas; Leclerc, Jean Luc; Boismare, Francis
CS Dep. Pharmacol., Hotel-Dieu
LO Rouen 76031, Fr.
SO Aviat., Space Environ. Med., 52(1), 19-23
SC 1-5 (Pharmacodynamics)
DT J
CO ASEMCG
IS 0095-6562
PY 1981
LA Eng

=> d 119 1-3 ti ab

L19 ANSWER 1 OF 3
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TI Neuroprotective effect of memantine demonstrated in vivo and in vitro
AB The protective effects of the anticonvulsant memantine against hypoxic or ischemic damage were studied in a rat model of transient

hemispheres. Ischemia was induced for 10 min by clamping both arteries and lowering the mean arterial blood pressure to 40 mmHg; the rats were allowed to recover for 7 days. Cultured neurons were made hypoxic with 1 mM NaCN added to the incubation medium for 30 min followed by a recovery period of 3 days. The effects of memantine were compared with those produced by a typical non-competitive N-methyl-D-aspartate antagonist, dizocilpine. Similar effects were obtained with both drugs. The drugs reduced the damage caused by transient ischemia to neurons of the hippocampal CA1 subfield. Memantine (10 and 20 mg/kg) had a dose-dependent effect when administered i.p. to rats 1 h before ischemia. Dizocilpine was active at 1 mg/kg. When administered after ischemia, 10 mg memantine/kg protected CA1 neurons against ischemic damage. The 2 drugs protected cultured neurons against hypoxic damage. The lowest effective concn. was 0.1 .mu.M dizocilpine and 1 .mu.M memantine. Thus, memantine possesses neuroprotective activity but is less potent than dizocilpine.

L19 ANSWER 2 OF 3
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TI Amantadine and derivatives as modifiers of x-rays on mammalian cells
AB The x-ray modifying effects of amantadine (I) and 2 of its derivs. [1-adamantyl-4-nitropyrazole (II) and 1-(3-hydroxy-1-adamantyl)-4-nitropyrazole (III)] were studied in hamster tumor cell cultures under oxic and hypoxic conditions. I showed a moderate radiosensitizing effect under hypoxic conditions whereas II had no radiomodifying effect. III exhibited a radiosensitizing effect under hypoxic conditions even in the presence of the radioprotectant DMSO. The radiosensitizing effect was attributed to the presence of the OH group.

L19 ANSWER 3 OF 3
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TI Dopaminergic agonists and conditioned avoidance response in normoxic or hypoxic rats
AB The actions of 4 dopaminergic agonists, apomorphine [58-00-4], bromocriptine [25614-03-3], amantadine [768-94-5], piribedil [3605-01-4] on a conditioned avoidance response were studied in normoxic or hypobaric hypoxic rats. Low doses of agonists have no effects in normoxia, but induce an antihypoxic protection (improvement of learning in hypoxia). In contrast, the higher doses impair learning both in normoxia and hypobaric hypoxia. The possibility of an antihypoxic property induced by dopaminergic postsynaptic receptors stimulation is discussed and seems to be the main phenomenon whereas action on other nonspecific sites seems to be responsible for the high dose-induced impairment of learning and of resistance to hypoxia.

=> s l20 not l19
L22 25 L20 NOT L19

=> s l20 not l18
L23 25 L20 NOT L18

=> d l23 1-25

L23 ANSWER 1 OF 25
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AN CA113(21):184729a
TI Preparation of arylamides for treatment of mental disorders
AU Usherwood, Peter Norman Russell; Bycroft, Barrie Walsham; Blagbrough, Ian Stuart; Mather, Alan John

LO UK
SO PCT Int. Appl., 34 pp.
PI WO 9002114 A1 8 Mar 1990
DS W: AU, DK, JP, US
AI WO 89-GB1004 30 Aug 1989
PRAI GB 88-20442 30 Aug 1988
IC ICM C07C235-34
    ICS A61K031-16; A61K031-165; C07C235-50; C07C235-60
SC 1-11 (Pharmacology)
SX 25
DT P
CO PIXXD2
PY 1990
LA Eng

L23 ANSWER 2 OF 25
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AN CA113(18):158675k
TI Dihydroxycinnamic acid amide derivatives and their pharmaceutical compositions for enhancement of nerve growth factor (NGF) production
AU Kishimoto, Toshimitsu; Ono, Takashi; Okumoto, Takeki; Arita, Masafumi
CS Yoshitomi Pharmaceutical Industries, Ltd.
LO Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
PI JP 02104560 A2 17 Apr 1990 Heisei
AI JP 89-158541 21 Jun 1989
PRAI JP 88-153839 22 Jun 1988
IC ICM C07C235-34
    ICS A61K031-165; A61K031-215; A61K031-40; A61K031-445; A61K031-495; A61K031-55; C07D207-09; C07D211-18; C07D223-04; C07D223-12; C07D227-04; C07D227-10; C07D295-18
SC 63-5 (Pharmaceuticals)
SX 2
DT P
CO JKXXAF
PY 1990
LA Japan

L23 ANSWER 3 OF 25
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AN CA113(17):145350a
TI Treatment of nueropsycho disorders with cyclopropanecarboxylates
AU Skolnick, Phil; Lewin, Anita; Marvizon, Juan Carlos; Monn, James; Rice, Kenner
CS National Institutes of Health
LO USA
SO U. S. Pat. Appl., 35 pp. Avail. NTIS Order No. PAT-APPL-7-390 745.
PI US 390745 A0 15 Jan 1990
AI US 89-390745 8 Aug 1989
SC 1-11 (Pharmacology)
DT P
CO XAXXAV
PY 1990
LA Eng

L23 ANSWER 4 OF 25
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AN CA113(9):78420h
TI Preparation and formulation of (tetrazolylalkyl)piperazinecarboxylic acid as excitatory amino acid receptor antagonists
AU Ornstein, Paul L.

LO USA
SO U.S., 7 pp.
PI US 4902687 A 20 Feb 1990
AI US 89-328348 27 Mar 1989
IC ICM A61K031-495
    ICS C07D403-06; C07D403-14
NCL 514253000
SC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT P
CO USXXAM
PY 1990
LA Eng

L23 ANSWER 5 OF 25
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AN CA113(9):77927s
TI Preparation of N,N'-disubstituted guanidines as excitatory amino acid antagonists
AU Weber, Eckard; Keana, John F.
CS Oregon Health Sciences University
LO USA
SO U.S., 11 pp. Cont.-in-part of U.S. Ser. No. 1,545.
PI US 4906779 A 6 Mar 1990
AI US 88-237367 29 Aug 1988
PRAI US 86-884150 10 Jul 1986
    US 87-1545 26 Jun 1987
IC ICM C07C129-12
NCL 564230000
SC 25-21 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
SX 1
DT P
CO USXXAM
PY 1990
LA Eng

L23 ANSWER 6 OF 25
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AN CA113(5):40474r
TI Preparation and formulation of 6-(acylmethyl)decahydrosisoquinoline-1- or -3-carboxylates as excitatory amino acid neurotransmitter antagonists
AU Ornstein, Paul L.
CS Lilly, Eli, and Co.
LO USA
SO U.S., 11 pp.
PI US 4902695 A 20 Feb 1990
AI US 89-309562 13 Feb 1989
IC ICM A61K031-47
    ICS C07D215-14; C07D215-36
NCL 514307000
SC 27-17 (Heterocyclic Compounds (One Hetero Atom))
SX 1, 29, 63
DT P
CO USXXAM
PY 1990
LA Eng

L23 ANSWER 7 OF 25
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AN CA113(1):6150x
TI Preparation of aminoalkylpyrroles as CNS agents

CS Cassella A.-G.
LO Fed. Rep. Ger.
SO Ger. Offen., 17 pp.
PI DE 3820190 A1 21 Dec 1989
AI DE 88-3820190 14 Jun 1988
IC ICM C07D207-34
    ICS C07D403-00; C07D207-42; C07D207-335; C07D207-337; C07D417-12;
         C07D417-06; A61K031-40; A61K031-415; A61K031-425; A61K031-55;
         C07D521-00
ICI C07D207-30, C07D333-04, C07D227-00, C07D309-00, C07D313-02,
     C07D337-02, C07D247-00; C07D207-30
SC 27-10 (Heterocyclic Compounds (One Hetero Atom))
SX 1
DT P
CO GWXXBX
PY 1989
LA Ger

L23 ANSWER 8 OF 25
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AN CA112(25):235290q
TI Preparation of 1,3-disubstituted pyrrolidines as serotonin (partial)
    agonists and antagonists
AU Schohe, Rudolf; Seidel, Peter Rudolf; Traber, Jorg; Glaser, Thomas
CS Bayer A.-G.
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 50 pp.
PI EP 338331 A1 25 Oct 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, NL, SE
AI EP 89-106023 6 Apr 1989
PRAI DE 88-3812989 19 Apr 1988
      DE 88-3835291 15 Oct 1988
IC ICM C07D417-06
    ICS C07D401-06; C07D207-12; C07D207-08; C07D207-09; C07D405-06;
         C07D403-12; A61K031-40; A61K031-41; A61K031-44
SC 26-7 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1
DT P
CO EPXXDW
PY 1989
LA Ger

L23 ANSWER 9 OF 25
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AN CA112(19):178657p
TI Preparation of 1,3,4,5-tetrahydrobenz[c,d]indoles as drugs
AU Junge, Bodo; Richter, Bernd; Glaser, Thomas; Traber, Joerg
CS Bayer A.-G.
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 50 pp.
PI EP 332960 A1 20 Sep 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 89-103871 6 Mar 1989
PRAI DE 88-3809155 18 Mar 1988
IC ICM C07D417-12
    ICS C07D209-90; C07D401-12; C07D403-12; A61K031-40; A61K031-425
SC 27-10 (Heterocyclic Compounds (One Hetero Atom))
SX 1
DT P
CO EPXXDW
PY 1989
LA Ger

AN CA112(13):110825g
TI Preparation and formulation of tetrazole excitatory amino acid receptor antagonists for treatment of nervous system disorders
AU Ornstein, Paul Leslie
CS Lilly, Eli, and Co.
LO USA
SO Eur. Pat. Appl., 25 pp.
PI EP 333033 A1 30 Aug 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 89-301337 13 Feb 1989
PRAI US 88-157760 19 Feb 1988
IC ICM C07D401-06
ICS A61K031-445; A61K031-41
ICI C07D401-06, C07D257-00; C07D211-00
SC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT P
CO EPXXDW
PY 1989
LA Eng

L23 ANSWER 11 OF 25

AN CA112(4):25677v
TI Axon-regenerating agents containing phosphatidylinositol, phosphatidylcholine, phosphatidylserine, and/or sphingomyelin
AU Arakawa, Yoshihiro; Tachibana, Shinro
CS Eisai Co., Ltd.
LO Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
PI JP 01135720 A2 29 May 1989 Heisei
AI JP 87-291783 20 Nov 1987
IC ICM A61K031-685
ICS A61K031-685
SC 63-6 (Pharmaceuticals)
SX 1
DT P
CO JKXXAF
PY 1989
LA Japan

L23 ANSWER 12 OF 25

AN CA111(17):151441f
TI Development and selective neurodegeneration in cell cultures from different hippocampal regions
AU Mattson, Mark P.; Kater, S. B.
CS Dep. Anat. Neurobiol., Colorado State Univ.
LO Fort Collins, CO 80523, USA
SO Brain Res., 490(1), 110-25
SC 14-10 (Mammalian Pathological Biochemistry)
DT J
CO BRREAP
IS 0006-8993
PY 1989
LA Eng

L23 ANSWER 13 OF 25

AN CA111(9):78023q

production, and cerebral dysfunction remedy comprising it as active ingredient
AU Iemura, Ryuichi; Hori, Manabu; Ohtaka, Hiroshi; Sukamoto, Takayuki; Hara, Hideaki; Ito, Keizo
CS Kanebo, Ltd.
LO Japan
SO Eur. Pat. Appl., 19 pp.
PI EP 302967 A2 15 Feb 1989
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-110691 10 Dec 1987
PRAI JP 87-200510 10 Aug 1987
IC ICM C07D239-95
ICS A61K031-505
SC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT P
CO EPXXDW
PY 1989
LA Eng

L23 ANSWER 14 OF 25
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AN CA111(9):78020m
TI Preparation of pharmaceutically active heterocyclic amines and their use for treating head injury, spinal trauma, stroke, etc.
AU McCall, John M.; Ayer, Donald E.; Jacobsen, E. Jon; Van Doornik, Frederick J.; Palmer, John R.
CS Upjohn Co.
LO USA
SO PCT Int. Appl., 173 pp.
PI WO 8808424 A1 3 Nov 1988
DS W: AU, DK, FI, JP, KR, NO, US
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE
AI WO 88-US1212 20 Apr 1988
PRAI US 87-43274 27 Apr 1987
IC ICM C07D401-14
ICS C07D239-50; C07D213-74; C07D405-12; C07D405-14; C07D251-40; C07D251-70; C07D267-14; C07D265-14; A61K031-35
SC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 25, 27
DT P
CO PIXXD2
PY 1988
LA Eng

L23 ANSWER 15 OF 25
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AN CA111(3):23387f
TI Preparation of 3-indolepyruvic acid derivatives and pharmaceutical use thereof
AU De Luca, Giovanna; Di Stazio, Giovanni; Margonelli, Andrea; Materazzi, Mario; Politi, Vincenzo
CS Polifarma S.p.A.
LO Italy
SO PCT Int. Appl., 26 pp.
PI WO 8809789 A2 15 Dec 1988
DS W: AU, BR, DK, FI, JP, KR, NO, US
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE
AI WO 88-IT41 1 Jun 1988
PRAI IT 87-48014 3 Jun 1987
IC ICM C07D209-18
ICS A61K031-405
SC 27-11 (Heterocyclic Compounds (One Hetero Atom))

DT P
CO PIXXD2
PY 1988
LA Eng

L23 ANSWER 16 OF 25
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AN CA110(15):135273b
TI Preparation of substituted imidazolylalkylpiperazines and -diazepines as pharmaceuticals
AU Pascal, Jean Claude; Lee, Chi Ho; Alps, Brian J.; Pinhas, Henri; Whiting, Roger L.; Beranger, Serge
CS Syntex Pharmaceuticals Ltd.
LO UK
SO Eur. Pat. Appl., 44 pp.
PI EP 289227 A1 2 Nov 1988
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 88-303646 22 Apr 1988
PRAI US 87-42181 24 Apr 1987
IC ICM C07D233-64
    ICS C07D403-06; A61K031-415; A61K031-435
SC 28-21 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1, 63
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 17 OF 25
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AN CA110(11):88637m
TI Method and compositions containing enantiomer of analgesic opioid agonist or antagonist for reducing neurotoxic injury
AU Choi, Dennis W.
CS Leland Stanford Junior University
LO USA
SO Eur. Pat. Appl., 8 pp.
PI EP 270290 A2 8 Jun 1988
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-310323 23 Nov 1987
PRAI US 86-934733 25 Nov 1986
IC ICM A61K031-485
SC 1-11 (Pharmacology)
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 18 OF 25
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AN CA110(1):893h
TI Treatment of cerebral disorder and skin disease by 1,3-dibutyl-7-(2-oxypropyl)xanthine
CS Beecham Group PLC
LO UK
SO Jpn. Kokai Tokkyo Koho, 6 pp.
PI JP 63079832 A2 9 Apr 1988 Showa
AI JP 87-227523 10 Sep 1987
PRAI GB 86-21869 11 Sep 1986
IC ICM A61K031-52
    ICS A61K031-52
ICA C07D473-06

DT P
CO JKXXAF
PY 1988
LA Japan

L23 ANSWER 19 OF 25
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AN CA109(21):190425g
TI Preparation of 5-aryl-3H-1,2,4-triazol-3-ones and their use in the treatment of neurodegenerative disorders
AU Miller, Francis P.; Kane, John M.; Sorensen, Stephen
CS Merrell Dow Pharmaceuticals, Inc.
LO USA
SO Eur. Pat. Appl., 10 pp.
PI EP 273309 A2 6 Jul 1988
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-118727 17 Dec 1987
PRAI US 86-944634 19 Dec 1986
    US 87-107001 16 Oct 1987
IC ICM A61K031-41
    ICS A61K031-44; A61K031-47
SC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
SX 1
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 20 OF 25
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AN CA109(9):73258u
TI Xanthine derivatives, their preparation and pharmaceutical compositions containing them
AU Nicholson, Charles David; Goering, Joachim; Morgan, Brian; Arch, Jonathan Robert Sanders
CS Beecham-Wuelfing G.m.b.H. und Co. K.-G.; Beecham Group PLC
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 19 pp.
PI EP 260127 A2 16 Mar 1988
DS R: BE, CH, DE, FR, GB, IT, LI, NL
AI EP 87-307978 9 Sep 1987
PRAI GB 86-21870 11 Sep 1986
IC ICM C07D473-04
    ICS A61K031-52
SC 26-9 (Biomolecules and Their Synthetic Analogs)
SX 1
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 21 OF 25
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AN CA108(23):204482s
TI Preparation of pyridoCl,2-alindoles for treatment of cerebrovascular disorders
AU Thielke, Dietrich; Hoeltje, Dagmar; Nadler, Guy
CS Beecham-Wuelfing G.m.b.H. und Co. K.-G.; Laboratoires Sobio S. A.
LO Fed. Rep. Ger.
SO Eur. Pat. Appl., 22 pp.
PI EP 252643 A1 13 Jan 1988
DS R: BE, CH, DE, FR, GB, IT, LI, NL

PRAI GB 86-16031 1 Jul 1986
GB 86-30634 22 Dec 1986
IC ICM C07D471-04
ICS A61K031-435
ICI C07D471-04, C07D221-00, C07D209-00
SC 27-10 (Heterocyclic Compounds (One Hetero Atom))
SX 1
DT P
CO EPXXDW
PY 1988
LA Eng

L23 ANSWER 22 OF 25
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AN CA107(7):54931a
TI Determination of regional glucose metabolism in brain by FDG and PET with reference to drug effects and changes in the course of cerebrovascular disease and dementia
AU Heiss, W. D.; Herholz, K.; Pawlik, G.; Beil, C.; Dal-Bianco, P.; Szelies, B.; Wienhard, K.
CS Max-Planck-Inst. Neurol. Forsch.
LO Cologne 5000/9, Fed. Rep. Ger.
SO Pharmacol. Cereb. Ischemia, Proc. Int. Symp., 87-98. Edited by: Krieglstein, Josef. Elsevier: Amsterdam, Neth.
SC 8-9 (Radiation Biochemistry)
SX 1, 14
DT C
CO 55NKAB
PY 1986
LA Eng

L23 ANSWER 23 OF 25
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AN CA106(21):174037q
TI Dysfunction of central cholinergic system in hyperkinetic rats, following postnatal anoxia
AU Speiser, Zipora; Sharafan, Chen; Bitter, Simon; Cohen, Sasson; Gonen, Baruch; Rehavi, Moshe
CS Sackler Fac. Med., Tel Aviv Univ.
LO Tel Aviv 69978, Israel
SO Adv. Behav. Biol., 29(Alzheimer's Parkinson's Dis.), 467-94
SC 14-10 (Mammalian Pathological Biochemistry)
DT J
CO ADBBBW
IS 0079-6246
PY 1986
LA Eng

L23 ANSWER 24 OF 25
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AN CA104(13):107124m
TI Phosphorus-31 nuclear magnetic resonance studies of anoxia and ischemia in animal brain and of human brain in Alzheimer's and Huntington's diseases
AU Cohen, M. M.; Kopp, S. J.; Pettegrew, J. W.; Minshew, N.; Krieglstein, J.; Glonek, T.
CS Rush-Presbyterian St. Lukes Med. Cent.
LO Chicago, IL, USA
SO Mal. Med./Drugs Dis., 1(3), 85-90
SC 14-0 (Mammalian Pathological Biochemistry)
DT J
CO MMDDEB

LA Eng

L23 ANSWER 25 OF 25
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AN CA102(17):146651j
TI Biological plasticity of the aging brain
AU Hoyer, Siegfried
CS Dep. Pathochem. Gen. Neurochem., Univ. Heidelberg
LO Heidelberg D-6900, Fed. Rep. Ger.
SO Top. Aging Res. Eur., 2(Aging Brain Senile Dementia), 23-42
SC 13-3 (Mammalian Biochemistry)
SX 14
DT J
CO TAEUEN
PY 1984
LA Eng

=> d l23 1-25 ti ab

L23 ANSWER 1 OF 25
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TI Preparation of arylamides for treatment of mental disorders
AB The title compds. Aa(C6H5-a)XbCONH(CH2)cND(CH2)dNE(CH2)f[NY(CH2)h]iNGJ [A = OH, alkoxy, cycloalkoxy, acyloxy, halo, etc.; a = 0-5; Y = C1-6 (un)substituted aliph. hydrocarbyl; b = 0, 1; c, d, f, h = 2 - 6; i = 0, 1; D, E, Y = H, C1-C4 alkyl, cycloalkyl; G, J, N = heterocyclyl] are effective for the treatment of celebral disorders, such as psychosis, senile dementia, and ischemia. To a soln. of 4-hydroxyphenylacetic acid in 1,2-dimethoxyethane (DME) was added a soln. of dicyclohexyl carbodiimide in DME and left at 25.degree. for 3 h. The ppt. was filtered and the filtrate and the washings were combined and a soln. of spermine was added and sealed under an atm. of N and allowed to stand at 25.degree. for 48 h and then concd. The residue was purified with column chromatog. and lyophilized to give N-(hydroxyphenylacetyl)spermine (I). The potency of I was tested as an antagonist of N-methyl-D-aspartate (NMDA)- and (RS)-.alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- induced response in a rat brain slice model. I at 10-5M decreased electrophysiol. recorded depolarization responses by22% for AMPA-induced one and 35% for NMDA-indeced one from the control level.

L23 ANSWER 2 OF 25
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TI Dihydroxycinnamic acid amide derivatives and their pharmaceutical compositions for enhancement of nerve growth factor (NGF) production
AB Pharmaceutical compns. contg. dihydroxycinnamic acid amides [I; R1, R2 = H, alkyl, acyl, aralkyl; R3, R4 = H, alkyl, aralkyl, Q; R5 = H, alkyl, cycloalkyl, (halo-, alkyl-, alkoxy-, and CF3-substituted) aryl, aralkyl, or aryloxyalkyl; m = 0 - 4; n = 1 - 3; or NR3R4 = heterocyclyl contg. O, S, or (substituted) NH] or their pharmaceutically acceptable acid addn. salts are useful for treatment and prophylaxis of central nervous system diseases or prevention of the progress of nerve cell disorders, e.g. Alzheimer's disease, senile dementia, or ischemic brain disorders. Eleven I in vitro stimulated 1.53 .+-. 0.07 to 3.43 .+-. 0.04 times the nerve growth factor prodn. in mouse fibroblastoma L-M cells as compared to that of the control. Generic tablet and capsule formulations contg. I are described.

L23 ANSWER 3 OF 25

TI Treatment of nueropsycho disorders with cyclopropanecarboxylates
AB The cyclopropanecarboxylates I [A = (un)substituted NH2; B = OH, OR1; R1 = substituted alkyl] and pharmaceutical salts thereof are drugs for the treatment of neuropsychopharmacol. disorders, assocd. with activation of the N-methylaspartate (NMDA) receptor complex. I are partial agonists of the strychnine-insensitive glycine modulatory site of the NMDA receptor complex. I (A = NH2, B = OH) (400 mg/kg) protected mice against convulsions induced by 125 mg NMDA/kg.

L23 ANSWER 4 OF 25
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TI Preparation and formulation of (tetrazolylalkyl)piperazinecarboxylic acid as excitatory amino acid receptor antagonists
AB The title compds. [I; R1 = CO2H, COR3, CONR42, SO2R3, etc.; R2 = H, C1-4 alkyl, (Ph)C1-4 alkyl; R3 = C1-16 alkoxy, (Ph)C1-4 alkoxy, etc.; R4 = H, C1-16 alkyl, (Ph)C1-4 alkyl, Ph; n = 2, 3] or their pharmaceutically acceptable salts, useful for treatment of epilepsy, stroke, anxiety, cerebral ischemia, muscular spasms, Alzheimer's disease, and Huntington's disease, were prepd. Pyrazinamide was hydrogenated over PtO2 and the resulting piperazine analog was N-alkylated by 4-bromobutyronitrile in EtOH, in the presence of Hünig's base and then treated with di-tert-Bu carbonate to give N-protected cyanopropylpiperazine II. Heating of II for 4 days at 80.degree. with Bu3SnN3 under N gave the appropriate tetrazole deriv. which was deprotected and the carbamoyl group hydrolyzed to give the title compd. I (R1 = CO2H, R2 = R4 = H, n = 3) (III) which in rats inhibited seizures induced by N-methyl-D-aspartate with a min. ED (MED) of 100 mg/kg. An analog of III (n = 2) had min. ED of 20 mg/kg in the same expt. Pharmaceuticals comprising I are given.

L23 ANSWER 5 OF 25
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TI Preparation of N,N'-disubstituted guanidines as excitatory amino acid antagonists
AB RNHC(:NH)NHR1 [I; R, R1 = (un)substituted alkyl, cycloalkyl, aryl, aralkyl] were prepd. as methylaspartate receptor ion-channel blockers useful as neuroprotective agents for treatment of, e.g., Alzheimer's disease. Thus, 3-EtC6H4NH2 was heated 15 min at 150.degree. with BrCN to give 20% I (R = R1 = 3-EtC6H4) which had IC50 of 168 and 62 nM against MK-801 and 1-[1-(2-thienyl)cyclohexyl]piperidine binding to rat brain membrane, resp.

L23 ANSWER 6 OF 25
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TI Preparation and formulation of 6-(acylmethyl)decahydroisoquinoline-1- or -3-carboxylates as excitatory amino acid neurotransmitter antagonists
AB The title compds. [I; X = CO2H, COR3, CONR24, CONHSO2R4, CONHCOR3, SO2R3, P(O)(OR4)2, tetrazolyl group Q; R3 = alkoxy, phenylalkyloxy, (un)substituted PhCH2O, alkanoyloxymethyl; R4 = H, alkyl, Ph, phenylalkyl; 1 of Y, Z = H, the other = CO2H, COR3, CONR24, CONHSO2R4, CONHCOR3, Q] were prepd. Thus, 4-HOC6H4CH2CH(NH2)CO2H was cyclocondensed with HCHO and the product converted in 4 steps to isoquinolonecarboxylate II (R = CO2Me, R1R2 = O, R5 = Et, which was refluxed 6 h in THF with [(EtO)2P(O)]2CH2 which had been treated with NaH to give II [R, R5 as above, R1R2 = CH2P(O)(OEt)2]. The latter was hydrogenated and the product deprotected to give II [R = R2 = R5 = H, R1 = CH2P(O)(OH)2] which had min. ED of 5 mg/kg i.p. for prevention of N-methyl-D-aspartate-induced seizures in neonatal

L23 ANSWER 7 OF 25
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1989

TI Preparation of aminoalkylpyrroles as CNS agents

AB The title compds. [I; R1, R2 = H, alkyl; R3 = H, alkyl, (modified) carboxylate; R4 = (modified) carboxylate, NO2, alkylsulfinyl, alkylsulfonyl, (substituted) phenylsulfinyl, phenylsulfonyl, PhCO, alkylcarbonyl, F3CCO, (NC)2CH, heterocyclylcarbonyl; R5 = aminoalkyl, acylaminoalkyl], were prepd. as nootropics (no data). Thus, MeCOCH2CO2Me was added slowly to AcNHCH2CH2NH2. ClCH2COMe was added and the mixt. was refluxed 20 h to give 44% pyrrolecarboxylate II.

L23 ANSWER 8 OF 25
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TI Preparation of 1,3-disubstituted pyrrolidines as serotonin (partial) agonists and antagonists

AB The title compds. [I; A = (fused) heteroaryl; B = cyano, CO2R1, CONR2R3, SO2NR2R3, SOmR4, NR5R6, C.tplbond.CCH2NR5R6; X = OCH2, CH2O, O; R1 = H, C1-12 alkyl, C5-8 cycloalkyl, C2-12 alkenyl, aryl, aralkyl; R2, R3 = H, C1-17 alkyl, (un)substituted aryl, etc.; R5,R6 = COR2, SO2R8, any of definitions for R2, R3; R7 = NHR9, C1-12 alkyl, C1-17 alkoxy, etc.; R8 = C5-8 cycloalkyl, (un)substituted C1-12 alkyl, (un)substituted (hetero)aryl, NR2R3; R9 = H, C5-8 cycloalkyl, (un)substituted C1-12 alkyl, aralkyl, (hetero)aryl, etc.; NR5R6 can form a (fused) heterocyclic ring, e.g., Q1, Q2, etc.; n = 1-10; m = 0-2] and their salts were prepd. as 5-hydroxytryptamine agonists, partial agonists (no data), and antagonists, useful for treatment of serotoninergic system-related CNS diseases. A mixt. of 3-(2-cyanophenoxy)pyrrolidine, 2-(4-bromobutyl)benzothiazol-3(2H)-one-1,1-dioxide, and Et3N in DMF was stirred 20 h at 45.degree. to give II which was converted to its oxalate. The latter in vitro antagonized serotonin with an inhibition const. Ki = 2 nM.

L23 ANSWER 9 OF 25
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TI Preparation of 1,3,4,5-tetrahydrobenz[c,d]indoles as drugs

AB The title compds. [I; R1 = H, alkyl, aralkyl, heteroarylalkyl; X = H, OMe, OH, SMe, halo, cyano, CONH2; Y = alkylene; Z = cyano, NR2R3, OR4, SOmR5, CO2R6, CONR7R8; R2, R3 = H, (cyclo)alkyl, alkenyl, (substituted) aryl, aralkyl, COR9, SO2R10; R2R3 = Q1, Q2, Q3, etc.; R4 = H, (cyclo)alkyl, alkenyl, aryl, aralkyl, acyl, alkoxycarbonyl, etc.; R5 = (cyclo)alkyl, alkenyl, (substituted) aryl, aralkyl, NR7R8; R6 = H, (cyclo)alkyl, alkenyl, aryl, aralkyl; R7, R8 = H, R6; R9 = H, amino, alkyl, alkoxy, (substituted) aryl, aralkyl, aralkoxy, heteroaryl; R10 = (substituted) alkyl, aryl, aralkyl, heteroaryl, NR7R8; m = 0-2], useful as central nervous system agents, were prepd. Thus, 6-methoxy-4-amino-1,3,4,5-tetrahydrobenz[c,d]indole and Et3N in DMFwere treated dropwise with 2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide in DMF and the mixt. was stirred 4 h at 50.degree. to give I [R1 = H, X = OMe, Y = (CH2)4, Z = Q1]. I bound to 5 HT1 receptors with IC values of 0.7-8 nmol/L. Several I showed antidepressant activity.

L23 ANSWER 10 OF 25
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TI Preparation and formulation of tetrazole excitatory amino acid receptor antagonists for treatment of nervous system disorders

AB The title compds. [I; R1 = CO2R3, CONR42, CONHSO2R3, CONHCOR3, O; R2 = H, C1-3 alkyl; n = 0-3; m = 0, 1; m + n = 0-3; R3 = H, C1-4 alkyl,

which are antagonists of excitatory amino acid receptors and thereby useful for the treatment of neural disorders (e.g. epilepsy, stroke, and anxiety) and neurodegenerative disorders such as Alzheimer's disease and Huntington's disease, are prepd. Thus, bromination of Me cis-4-(2-hydroxyethyl)-N-tert-butoxycarbonyl-2-piperidinecarboxylate with Ph3PBr2 in CH2Cl2 followed by cyanation with NaCN in DMSO gave Me cis-4-(2-cyanoethyl)-N-butoxycarbonyl-2-piperidinecarboxylate which was heated 48 h at 80.degree. with Bu3SnN3 to give, after hydrolysis with 6NHCl, cis-(I)-4-[2-[1(2)-H-tetrazol-5-yl)ethyl]-2-piperidinecarboxylic acid. I blocked N-methyl-D-aspartic acid-induced lethality in mice with min. ED of 10-160 mg/kg i.p.

L23 ANSWER 11 OF 25
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TI Axon-regenerating agents containing phosphatidylinositol, phosphatidylcholine, phosphatidylserine, and/or sphingomyelin

AB Axon-regenerating agents contain natural or synthetic phosphatidylinositol, phosphatidylcholine, phosphatidylserine, and/or sphingomyelin. Dipalmitoylphosphatidylcholine at 100 .mu.g/mL exhibited remarkable axon regeneration. An injectable emulsion was formulated contg. phosphatidylcholine-contg. egg yolk phospholipid 6, soybean oil 5%, and glycerin 12.5 g.

L23 ANSWER 12 OF 25
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TI Development and selective neurodegeneration in cell cultures from different hippocampal regions

AB Previous studies have shown that pyramidal neurons in hippocampal regions CA1 and CA3 are selectively vulnerable in several neurodegenerative disorders and that a subpopulation of pyramidal neurons in cell cultures of embryonic hippocampus are sensitive to glutamate neurotoxicity. To det. whether the patterns of cell loss seen in situ correlate with intrinsic differences in neuronal sensitivities to glutamate-induced degeneration acquired during development, the authors characterized cultures established from different regions of postnatal rat hippocampus and then examd. neuronal sensitivity to glutamate. Tissue corresponding to the dentate gyrus (DG) and regions CA1, CA2, and CA3 of Ammon's horn was removed by microdissection from transverse hippocampal slices and was used to establish cultures of dissocd. cells. Cultures from all 4 regions contained 3 major morphol. classes of neurons; pyramidal-like, bipolar, and stellate. Pyramidal-like neurons comprised the majority of neurons in all cultures; these neurons extended one long and branching axon, and one or more short dendrites. Immunocytochem. showed that all neurons possessed high levels of glutamate-like and GABA-like immunoreactivity when grown in isolation. In contrast, when bipolar and pyramidal neurons were cultured in contact with glial cells, glutamate and GABA immunoreactivity were selectively reduced in the bipolar and pyramidal cells, resp., suggesting that cell interactions influence neurotransmitter phenotype. Subpopulations of hippocampal neurons from each hippocampal region were vulnerable to glutamate-induced neurotoxicity. Bipolar and stellate cells were resistant to glutamate, whereas pyramidal-like neurons showed varying degrees of sensitivity to glutamate depending upon which region they were taken from. Expts. with specific glutamate receptor agonists and antagonists demonstrated that both non N-methyl-D-aspartic acid (NMDA) receptors and NMDA receptors mediated glutamate-induced degeneration. There were clear differences in the vulnerability of the pyramidal-like neuron populations in cultures from the different hippocampal regions. The rank order of the vulnerability of

between regions in culture was: DG<CA2<CA3<CA1. This pattern of selective vulnerability in cell culture corresponds directly to the pattern of selective cell loss seen in situ in Alzheimer's disease, epilepsy, and stroke suggesting that intrinsic neuronal differences in glutamate sensitivity may be involved in these disorders.

L23 ANSWER 13 OF 25
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TI 2-(4-Allyl-1-piperazinyl)-4-pentyloxyquinazoline, processes for its production, and cerebral dysfunction remedy comprising it as active ingredient

AB Quinazoline deriv. I [R = (CH2)4Me, R1 = Q] (II) useful as cerebral dysfunction remedy, was prepd. by, e.g., reaction of I (R = Cl, R1 = Q) (III) with Me(CH2)4OH. POCl3 (10 mL) was added to 10 g 2-(4-allyl-1-piperazinyl)-4(3H)-quinazolinone (IV) (prepn. given) and the mixt. was refluxed 3 h to give 10 g III. To a suspension of 3.0 g III in DMF, were added 1 l-pentanol and 0.5 g NaH under ice-cooling and then the mixt. was stirred 4 h at room temp. to give II. II.2HCl showed the activity of inhibiting formation of lipid peroxide (antioxidant activity) with an IC50 of .52 .mu.M which was detd. by the amt. of malonaldehyde formed in rats. Tablets (200 mg) were prepd. from II.2HCl 100, lactose 890, cryst. cellulose 900, CM-cellulose Ca 70, talc 25, and Mg stearate 15 g.

L23 ANSWER 14 OF 25
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1988

TI Preparation of pharmaceutically active heterocyclic amines and their use for treating head injury, spinal trauma, strokes, etc.

AB The arom. amines, alkylamines, bicyclic amines, cycloalkylamines, arom. bicyclic amines, hydroquinoneamines, amino ethers, and bicyclic amino ethers, which are individually represented by Markush formula, e.g. bicyclic amines I [W = O, S, NH, C1-3 alkylimino; n = 0, 1, or 2; R7 = H, C1-4 alkyl, C1-4 alkyl, C1-4 alkylcarbonyl, PhCO, prodrug (e.g. PO2O-, COCH2CONHCH2SO2O-, or COCH:CHCO2-); R10 - R12 = H, Me; when R25 = R26 = H, R16 = .alpha.-R17:.beta.-R18 where one of R17 and R18 = H, Me, Et, or Ph and the other is COM (M = substituted NH2, heterocyclic amino; or C:CQN:NCQ:CH where Q = 2-pyridinyl), (CH2)pCOM (p = 1-6), (CH2)qM (q = 1-6) or CO2(CH2)rM (r = 2-6); when n = 0, R16 = R19:R20 where one of R19 and R20 taken together with R25 forms a second bond betweens the C atoms to which R16 and R25 are attached and the other = M-substituted groups described for R16; when n = 1, R25R26 = bond between the C atoms to which R25 and R26 are attached; the original Markush definition was not completed.], useful as pharmaceuticals for treatment of head injury, spinal trauma, stroke and a no. of other related injuries and conditions (no data), are prepd. A mixt. of 6-bromohexanol, 2,6-bis(1-pyrrolidinyl)-4-(1-piperazinyl)-1,3,5-triazine, K2CO3, and NaI in MeCN was refluxed to give 4-[4,6-bis(1-pyrrolidinyl)-1,3,5-triazin-2-yl]-1-piperazinehexanol.

L23 ANSWER 15 OF 25
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TI Preparation of 3-indolepyruvic acid derivatives and pharmaceutical use thereof

AB The title compds. II; X = C1-4 alkoxy, cyclohexyloxy, PhCH2O, C1-4 (di)alkylamino, (di)cyclohexylamino, PhCH2NH, (PhCH2)2N, amino acid residue], useful as central nervous system (CNS) agents, are prepd. Hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl were added to a soln. of I (X = OH) in THF under Ar and cooling, followed by Me2NH.HCl and 4-methylmorpholine to give 35% amide I (X = Me2N). In an audiogenic convulsion test, I (X = OH) and its Mg salt showed 33%

with tryptophan and 65% with controls. I also protected against N-methyl-D-aspartic acid-induced convulsion at 1 g/kg i.p. in mice, with a death rate of 3/7, vs. 8/10 of controls.

L23 ANSWER 16 OF 25
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TI Preparation of substituted imidazolylalkylpiperazines and -diazepines as pharmaceuticals

AB Title compds. I (R1,R4,R5 = aryl; R2 = aryl, alkyl, H; R3 = alkyl, OH, H; m = 2, 3; n = 0-2, or n = 0, 2 when R3 = OH; q = 0-3) useful as Ca entry blockers (no data) are prepd. To a refluxing soln. of N-(diphenylmethyl)piperazine and NaOH in EtOH-H2O (3:2) was added a soln. of 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole.HCl (prepn. given) in EtOH-H2O (3:2) to give 70% I (R1 = p-MeC6H4; R2 = Me; R3 = H; R4 = R5 = Ph; m = 2; n = q = 0) (II). II.3HCl at 5 mg/kg p.o. showed .apprx.5.7, .apprx.9.5, and .apprx.11.8 mL urine collected after 1, 3, and 6 h, resp. of administration in normotensive rats, vs. .apprx.3.3, .apprx.7.3, and .apprx.5.6 mL for control, resp. and no significant kaliuretic effects were obsd. A tablet was formulated contg. I 25, cornstarch 20, lactose 153, and Mg stearate 2 mg.

L23 ANSWER 17 OF 25
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TI Method and compositions containing enantiomer of analgesic opioid agonist or antagonist for reducing neurotoxic injury

AB The adverse effects of neurotoxic malfunction are reduced by administration of an effective amt. of a mirror-image enantiomer of an analgesic opioid agonist or antagonist, esp. an opiate agonist having ring system I. Mixed cortical cell cultures, contg. both neuronal and glial elements were prepd. Exposure to 0.5 mM glutamate for 5 min resulted by the following day in disintegration of the majority of the neurons; many remaining neurons failed to exclude trypan blue dye. However, when dextrorphan (100 .mu.M) was added to the glutamate exposure soln., both the morphol. and the chem. evidence of glutamate neurotoxicity was markedly attenuated. Neurons protected by addn. of dextrorphan excluded trypan blue dye and remained morpholog. stable for at least several days.

L23 ANSWER 18 OF 25
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TI Treatment of cerebral disorder and skin disease by 1,3-dibutyl-7-(2-oxypropyl)xanthine

AB The title compd. (I) is useful in the treatment of cerebral disorders (e.g., dementia, Alzheimer's disease, etc.) and skin disease. I administered to rats restored the expti. induced memory damage, indicating that I is effective in treating dementia and other disorders.

L23 ANSWER 19 OF 25
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TI Preparation of 5-aryl-3H-1,2,4-triazol-3-ones and their use in the treatment of neurodegenerative disorders

AB The title compds. (I; R = Cl-6 alkyl, alkoxy, OH, halo, CF3; R1 = H, Cl-6 alkyl; R2 = Cl-6 alkyl; X = Ph, naphthyl, heteroaryl; RnX = methylenedioxyphenyl; n, m = 0-2), useful for treatment of brain disorders (no data), were prepd.
1-(2-Thienoyl)-4-methylsemicarbazide (prepn. given) was refluxed 23 h in 1 N aq. NaOH to give
5-(2-thienyl)-2,4-dihydro-4-methyl-3H-1,2,4-triazol-3-one.

TI Xanthine derivatives, their preparation and pharmaceutical compositions containing them

AB Xanthine derivs. I [R1, R2 = Bu, (CH2)2CH(OH)Me, (CH2)2CH(OH)CH2OH, (CH2)2COMe, (CH2)2C(OR4)(OR5)Me; R4, R5 = C1-4 alkyl; R4R5 = C2-4 polymethylene (R1, R2 not both Bu); R3 = CH2CH(OH)Me, CH2COMe, CH2C(OR6)(OR7)Me; R6, R7 = C1-4 alkyl; R6R7 = C2-4 polymethylene] and their salts, were prepd. I have a protective effect against the consequences of cerebral metabolic inhibition and also improve data acquisition or retrieval following transient forebrain ischemia. I are also active in increasing the O2 tension in ischemic skeletal muscle. I also act as phosphodiesterase inhibitors and elevate cAMP levels. 3-Butylxanthine was alkylated with ClCH2COMe and NaOEt in EtOH to give 30.6% 3-butyl-1-(2-oxopropyl)xanthine which was acetalized with (HOCH2)2 to give 2-methyl-2-[(3-butylxanthin-7-yl)methyl]-1,3-dioxolane. Reacting with ClCH2CH2COMe and K2CO3 in DMF gave 2-methyl-2-[[1-(3-oxobutyl)-3-butylxanthin-7-yl]methyl]-1,3-dioxolane which was deacetalized to give 1-(3-oxobutyl)-3-butyl-7-(2-oxopropyl)xanthine. NaBH4 redn. gave 1-(3-hydroxybutyl)-3-butyl-7-(2-hydroxypropyl)xanthine (II). At 2 times 30 mg/kg in rats, II gave 40% redn. in Et3Sn-induced cerebral edema formation.

L23 ANSWER 21 OF 25

TI Preparation of pyrido[1,2-a]indoles for treatment of cerebrovascular disorders

AB The title compds. [I; R1 = H, C1-6 alkyl, C1-6 alkoxy, halo; R2, R3 = H, R2R3 = bond; R4, R5 = H; R4R5 = O; R6 = (un)substituted Ph, substituted phenylalkyl, substituted phenylalkanoyl; R7 = H; C1-4 alkyl] and their salts were prepd. 10-[2-[4-(Methoxycarbonylmethylamino)benzoyl]aminoethyl]-6,7,8,9-tetrahydropyrido[1,2-a]indole-HCl (obtained in 5 steps from 6,7,8,9-tetrahydropyrido[1,2-a]indole-10-propionic acid), in THF, was added to LiAlH4 and refluxed to give I [R1, R4, R5, R7 = H; R2R3 = bond; R6 = 4-(HOCH2CH2NH)C6H4CH2.cntdot.2HCl] (II). Rats intoxicated with 2 mg Et3SiCl/kg once a day for 5 days and also given II orally twice daily as aq. soln. or suspension at a dose 1 mL/100 g body-wt. showed a protection index of 47%.

L23 ANSWER 22 OF 25

TI Determination of regional glucose metabolism in brain by FDG and PET with reference to drug effects and changes in the course of cerebrovascular disease and dementia

AB The detn. of cerebral regional glucose metab. in brain by positron emission tomog. (PET) with [18F]fluoro-2-deoxy-D-glucose (FDG) was studied in healthy volunteers and in patients with acute cerebrovascular disease, intracerebral hemorrhage, dementia, and ischemic stroke. A mean glucose consumption rate of 29-32 .mu.mol/100g/min was obsd. in healthy volunteers, with the highest values being found in the visual cortex (45-50 .mu.mol/100g/min) and striatum (42-46 .mu.mol/100g/min) and lowest in the white substance (15-22 .mu.mol/100g/min). Changes in glucose metab. in the course of disease are traced, and changes during therapeutic intervention described.

L23 ANSWER 23 OF 25

TI Dysfunction of central cholinergic system in hyperkinetic rats,

AB Single exposure of rats to postnatal anoxia caused a long lasting dysfunction of the cholinergic system as expressed by a gradual decline in choline acetyltransferase (ChAT) activity throughout development and maturity. Decreased levels or released acetylcholine during development and maturity could cause a compensatory increase in postsynaptic receptors, hyperkinesia, and learning deficits, all these being changes found in the anoxia rats during their development. The decline in ChAT activity which is presently found in the hippocampus and caudate is probably not restricted to these 2 areas; that other cholinergic areas in the brain are also affected by anoxia is assumed. The first compensatory response to decreased levels of acetylcholine is the increase in d. of postsynaptic muscarinic receptors, which maturate relatively earlier than the presynaptic enzymes. With further development, however, a compensatory increase in choline uptake was found with return to normal behavior and a decrease in postsynaptic receptor d. to normal values. A lack of a compensatory increase in choline uptake in some brain areas other than the hippocampus, or its decline with age, may cause severe dysfunction of the cholinergic system, esp. in old age. Anoxia-treated rats may therefore serve as a model for Alzheimer disease in which there is a dysfunction of the central cholinergic system.

L23 ANSWER 24 OF 25
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TI Phosphorus-31 nuclear magnetic resonance studies of anoxia and ischemia in animal brain and of human brain in Alzheimer's and Huntingtgn's diseases
AB A review with 10 refs. of the changes occurring in the brain concns. of various phosphates in the title diseases.

L23 ANSWER 25 OF 25
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TI Biological plasticity of the aging brain
AB Normal cerebral aging is assocd. with significant redns. of the concns. of glucose, fructose 1,6-diphosphate, pyruvate, malate, ATP, and creatine phosphate in brain cortex of male Wistar rats. The effect of a 15-min severe arterial hypoxemia on glucose and energy metab. of the aging brain yield similar results in 2-yr-old rats and 1-yr-old controls. Severe arterial hypoxemia, however, seems to cause less pronounced reactions in glycolytic flux and citric acid cycle intermediates. A 15-min complete cerebral ischemia produced changes which were in general similar in 1- and 2-yr-old rats. Evidently the aging brain suffers from the capacity to meet the demands under stress situations such as severe arterial hypoxemia and ischemia, i.e. the plasticity of the aging brain is reduced. A 3-wk i.p. application of vincristine induced changes in the glycolytic breakdown of glucose in brain cortex comparable to those which are found in dementia of Alzheimer type. This animal model may be a useful tool for dementia research.

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